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| 09/216,604 | 12/17/1998 | YAJUN GUO | | 9403 |

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| EXAMINER | |
|---|---|
| EWOLDT, GERALD R | |
| ART UNIT | PAPER NUMBER |
| 1644 | 19 |

DATE MAILED: 10/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/216,604 | Applicant(s) Guo |
|---|---|---|
| | Examiner G.R. Ewoldt | Art Unit 1644 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *1/22/02 and 7/22/02* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *85-90* is/are pending in the application.

4a) Of the above, claim(s) *86-90* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *85* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

**DETAILED ACTION**

1. The request filed on 1/22/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/216,604 is acceptable and a CPA has been established. An action on the CPA follows.

2. Applicant's election of Group I, Claim 85, and the species: "tumor cell" as the specific diseased cell type and "CD28:gp55 bispecific antibody" as the specific bridge molecule, in Paper No. 18, filed 7/22/02, with traverse, is acknowledged. Applicant argues that there would be no additional search burden involved in searching Group II, Claim 86, together with Claim 85, as the claims have identical classes and subclasses. Applicant is advised that the class and subclass search comprise just a portion of a biotechnology search. Additional databases such as Medline comprise the bulk of said search. As the method of Group II comprises an additional step, i.e., the treating of the diseased cells, said method likely resulting in a different product, said method is patentably distinct.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 86-90 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claim 85 is being acted upon. Applicant is advised that the genus of bridge molecules has been expanded to include a CD28:gp115 bispecific antibody.

4. In view of Applicant's Amendment, filed 1/22/02, in which all previously pending claims were canceled and replaced, followed by the election of an invention patentably distinct from the invention previously under examination, all previous rejections have been withdrawn and Applicant's Remarks have been rendered moot.

5. The following are new grounds for rejection.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 85 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Under *Vas-Cath, Inc. v. Mahurkar* , 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention, and that the invention, in that context, is whatever is now claimed.

There is insufficient written description to show that Applicant was in possession of a bridge molecule, other than a bispecific monoclonal antibody. The specification discloses that a bridge molecule encompasses "bispecific monoclonal antibodies, fusion proteins, organic polymers, and hybrids of chemical and biochemical materials." Said definition must clearly be considered to encompass an essentially unlimited genus. However, the specification discloses examples only of bispecific monoclonal antibodies. No specific fusion proteins, organic polymers, nor hybrids of chemical and biochemical materials, suitable for use in the method of the instant claim are disclosed. Given the breadth of the claim, one of skill in the art must conclude then that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

8. Claim 85 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of preparing an immunogenic composition, comprising the steps of: providing an autologous tumor cell, incubating said cell in IFNγ and TNFα, providing a CD28:gp115 or CD28:gp55 bispecific monoclonal antibody bridge molecule, attaching the bridge molecule to the tumor cell, and collecting a pharmaceutically effective amount of the target diseased cell with the attached bridge molecule,

does not reasonably provide enablement for:

a method of preparing an immunogenic composition, comprising the steps of: providing an autologous target diseased cell, increasing concentration of primary T cell activation molecules or costimulatory T cell activation molecules in the target diseased cell, providing a bridge molecule including one or more binding sites for one or more costimulatory molecules on a surface of one or more T cells of a patient mammal, attaching the bridge molecule to the target diseased cell, and collecting a pharmaceutically effective amount of the target diseased cell with the attached bridge molecule.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding the breadth of the claims, the specification defines a target diseased cell as any "cell causing, propagating, aggravating, or contributing to a disease in a patient mammal." Clearly said definition encompasses not only tumor and pathogen infected cells, but completely normal cells under many conditions. For example, normal T cells would be considered well-known contributors to inflammation and normal mast cells are well-known aggrevators allergy. Following the same line of reasoning, capillary endothelial cells would be well-known contributors to atherosclerosis. The induction of an immune response to any of these normal cell types would not likely be considered therapeutically acceptable, thus, a method of preparing a pharmaceutical composition for said induction must be considered highly unpredictable as the specification has not taught how to use said composition. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

Further regarding the breadth of the claims, part (c) of the claim recites that the bridge molecule need bind only "one or more costimulatory molecules on a surface of one or more T cells" (presumably to provide a required costimulatory activation signal). The specification discloses that a "costimulatory molecule" can be essentially *any* CD marker from CD1a to CDw130.

First, it must be noted that many of the disclosed markers are never expressed by T cells, for example CD19 (a B cell marker) and CD83 (a dendritic cell marker). Thus, a method that includes a binding step that could not happen must be considered highly unpredictable. Second, even certain markers that are expressed on T cells, such as CD4 or CD8, play no part in costimulation, indeed the activation of markers such as CD4 or CD8 alone is well-known in the art to induce T cell anergy, i.e., the opposite effect from stimulation (see for example, Janeway et al., 1994).

Regarding the working examples of the specification, it is noted that at least one of the target diseased cells absolutely *requires* cytokine induction to be immunogenic (specification page 23, Hepa 1-6 tumor cells are incapable of inducing an immune response even after the increasing of T cell activation molecule B7). However, cytokine induction is not a recited method step of the instant claims. Accordingly, it appears then that the method of the instant claims cannot function in at least one of the disclosed examples to prepare an immunogenic composition as claimed, thus, rendering the method of the instant claim again, highly unpredictable. Given said unpredictability, the method of the instant claims must again be considered to require undue experimentation.

*In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claim 85 is rejected under 35 U.S.C. 102(b) as being anticipated by Shi et al. (1996, previously of record).

Shi et al. teaches a method of preparing an immunogenic composition, comprising the steps of: providing an autologous target diseased cell (human liver cancer cells), increasing

concentration of primary T cell activation molecules or costimulatory T cell activation molecules in the target diseased cell (treatment with cytokines), providing a bridge molecule including one or more binding sites for one or more costimulatory molecules on a surface of one or more T cells of a patient mammal (a CD28:gp115 bispecific antibody), attaching the bridge molecule to the target diseased cell, and collecting a pharmaceutically effective amount of the target diseased cell with the attached bridge molecule. Note that in the reference the diseased cells were used to activate TILs or PBLs *in vitro*, however, it would have been an inherent property of said activation that the diseased cells would have been collected before said *in vitro* activation.

The reference clearly anticipates the claimed invention.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

G.R. Ewoldt, Ph.D.
Patent Examiner
Technology Center 1600
October 10, 2002